Subcommittee on Criminal Justice, Drug Policy and Human Resources
Statement by Diane Beeson, PhD
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Chairman Souder, Representative Waxman, and Members of the Committee, thank you for inviting me to testify today on exploitation, fraud, and ethical problems related to human embryo cloning and embryonic stem cell research.

My name is Diane Beeson. I am a medical sociologist and Professor Emerita of Sociology at California State University, East Bay. I received my PhD at the University of California, San Francisco (UCSF) and was a Pew Postdoctoral Research Fellow at UCSF's Institute for Health Policy Studies. I have a long-standing professional interest in reproductive genetics and have worked at UC Berkeley's Center for the Study of Social Change on several federally funded studies on the social implications of genetic technologies. I have also been a Visiting Fellow at Stanford University's Center for Bioethics and have served on many review committees for the Human Genome Research Institute's Ethical, Legal and Social Implications Research Program. I am currently an affiliated scholar with the Institute on Biotechnology and the Human Future at the Illinois Institute of Technology and the Chicago-Kent College of Law.

First, I would like to emphasize that I am a life-long supporter of women's abortion rights and I support embryonic stem cell research using embryos left over from IVF treatments. However, in 2004 when the California Stem Cell Initiative was placed on the ballot asking voters to authorize $3 billion in state bonds for research that prioritized the development of human cloning technologies, I decided to speak publicly about my concerns and became a founder of the Pro-Choice Alliance Against Proposition 71.

Like many social scientists I have broad concerns related to the wisdom of developing cloning technologies. However, my comments today will focus on social and ethical problems created by the demand for human eggs needed in experimental cloning, a process also known as somatic cell nuclear transfer, or SCNT. Specifically, the concerns I will raise today are related to the exploitation of women necessary for the development of SCNT. These are the same problems that have been uncovered in the scandal surrounding Dr. Hwang's research and that we can expect to persist wherever SCNT is pursued.

Dr. Hwang Woo-suk's original claim to have successfully used SCNT to create a human embryo from which stem cells were extracted was first announced in February 2004. California was then in the early stages of a $35 million political campaign and media blitz to assure voters that if they supported massive public funding of this research miracle cures would soon be available for an unlimited list of lethal disorders.

Initial reports indicated Hwang's team used 242 human eggs to create one embryo in 2004. Then in 2005 he claimed to have generated "11 patient-specific stem-cell lines with a success rate of 1 line for approximately every 20 oocytes."[1] This created the illusion that significant progress had been made in bringing down the number of eggs SCNT would require. It has now been revealed that Dr. Hwang used over 2000 eggs in his discredited research.[2] His failure to produce even one cloned embryo reminds us that we still do not know how many thousands, or possibly even millions of eggs it may require to perfect SCNT. Furthermore, it has become clear that payment, coercion, and lying were used to acquire the eggs that we were told many women were eager to donate.

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[1] Snyder, E.Y. and J.F. Loring. Beyond Fraud—Stem-Cell Research Continues. *New England Journal of Medicine* 2006; Vol. 354, No. 4, pp. 321-324.
[2] Steinbrook, R. Egg Donation and Human Embryonic Stem Cell Research. *New England Journal of Medicine* 2006; Vol. 354, No. 4, pp. 324-326.

Californians, influenced by irresponsibly inflated claims of imminent cures, reinforced by excitement over Hwang's fraudulent research successes, have already cast their votes to massively fund SCNT; but the public has yet to be adequately informed about the human costs of such research. Today I would like to make three points in that regard:

1. Egg extraction as currently practiced poses inadequately understood, yet clearly significant, risks to the health of women.

2. Under current conditions informed consent to participate in egg extraction for research purposes is not possible.

3. The same social conditions that drive the demand for women's eggs set the stage for other violations of the public trust.

In light of this situation, I support the call for a moratorium on SCNT. This is a position supported by the feminist pro-choice women's health organization, Our Bodies, Ourselves, the California Nurses Association,[3] and many other pro-choice progressives.

To explain my position, let me begin with a brief background on egg extraction. Because such practices have come into expanded use since the birth of the nation's first test tube baby in December 1981, it is widely assumed that they have been proven to be safe. Unfortunately, this is not the case.

Extraction of multiple eggs involves both ovarian suppression and what is known as "ovarian hyperstimulation" using powerful hormones into a woman's body to manipulate it into producing many—often a dozen or more—eggs at a time rather than the normal one or two. The mature eggs are then collected for use in infertility treatments, in vitro fertilization, or research.

Contrary to common assumptions, these procedures have not been adequately studied. For example, one drug commonly used in egg extraction, Lupron, has not been approved for this purpose, but rather is used off label. Another such drug, Antigon, has been approved for such use, but no data are available on its long-term safety.[4]

As Suzanne Parisian, former Chief Medical Officer of the Food and Drug Administration, explains, "Pharmaceutical firms have not been required by either the government or physicians to collect safety data for IVF drugs regarding risk of cancer or other serious health conditions despite the drugs having been available in the United States for several decades." [5]

The FDA currently has on file over 6000 complaints regarding Lupron, including 25 reported deaths.[6] These complaints must be investigated and analyzed.

In the absence of long-term follow-up it is impossible to assess accurately the seriousness of the risks to women's health from the expanding use of egg extraction. One study reports that up to 14 percent of patients undergoing ovarian hyperstimulation experience some form of ovarian hyperstimulation syndrome, or OHSS.[7] This is a condition whose pathophysiology remains unclear. Common symptoms of

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[3] See Appendix A. California Nurses Association Position Statement on Embryonic Stem Cell Research.
[4] See Appendix B. Letter from Dr. Suzanne Parisian, Former Chief Medical Officer, FDA. Also on-line at http://www.genetics-and-society.org/resources/items/200502_letter_parisian.html.
[5] See Appendix B.
[6] Lazar, Kay. Wonder Drug for Men Alleged to Cause Harm in Women. *Boston Herald*, August 22, 1999.
[7] Hugues, in Vayena, E. *et al.* (eds). *Current Practices and Controversies in Assisted Reproduction.* World Health

mild OHSS include abdominal discomfort, ovarian enlargement, nausea and vomiting. Those who develop severe OHSS may experience a wide range of serious conditions including loss of future fertility, kidney or multiple organ failure, and death. The frequency of severe OHSS is estimated to be as high as 10 per cent of women who undergo the procedure.[8]

We don't yet know the full extent of the damage to the health of the Korean women who provided the eggs used by Dr. Hwang. But we do know that a coalition of 35 women's groups is suing the South Korean government on behalf of women who have been harmed in the process of egg extraction. Reports are that about 20 percent of the donors have experienced side-effects.[9] We also know that serious problems with egg extraction are not unique to the Korean experience.

Jacqueline Rushton, who died as a direct result of OHSS in Dublin, Ireland, in 2003, suffered a gradual deterioration of her organs, virtually all of which were slowly destroyed.[10] Temilola Akinbolagbe, a young woman who died last April in London, suffered a more sudden death from a massive heart attack linked directly to OHSS.[11]

While such events seem to be rare, it is possible that many deaths and other longer-term side effects of ovarian hyperstimulation have simply not been linked officially to the egg extraction procedures that preceded them. For example, Dr. Parisian reminds us that "studies to date have not ruled out a possible link between stimulation drugs and increased risk of ovarian cancer." She concludes that it is very likely that "those promoting SCNT research may be unknowingly tackling a far more costly and serious health burden by allowing the expanded use of current IVF stimulation drugs for SCNT." [12]

One of most destructive consequences of ovarian hyperstimulation for women may be serious abnormalities in their children. Just this month a new study reports that ovarian hyperstimulation treatment in mice results in several significant abnormalities in their later offspring. These effects include growth retardation, a delay in ossification (bone development) and an eight-fold increase in a significant rib deformity. This particular deformity in humans is associated with an increased incidence of abnormalities and cancer. Because of these associations, the authors conclude that it is possible that their findings may have implications for the use of ovarian hyperstimulation treatments in women. This question must be answered before involving thousands of women in ovarian hyperstimulation purely for research purposes.[13]

Scientists and other proponents of SCNT have been reluctant to confront forthrightly the dangers related to egg extraction. This reluctance has been demonstrated repeatedly in recent California politics. For example, during the campaign to pass Proposition 71 its proponents took legal action in an effort to

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Organization, Geneva, Switzerland, pp 102-125 (2002).

[8] Magnus, D. and M.K. Cho. Issues in Oocyte Donation for Stem Cell Research. *Sciencexpress/www.sciencexpress.org* May 19, 2005, p.1.

[9] Hwa-young, Ova Donors Demand Compensation from Government. *AsiaNews.it.* 2-7-2006. www.asianews.it/view_p.php?1=en&art=5322

[10] See Appendix C. Letter from Rushton's mother. Mrs. Angela Hickey.

[11] Woman died after starting IVF treatment. Richmond & Twickenham Times. 20 April 2005. http://www.richmondandtwickenhamtimes.co.uk/mayor/other/display.var.589076.0.0.php

[12] See Appendix B

[13] Steigenga, MJ, et al. Evolutionary Conserved Structures as Indicators of Medical Risk: Increased Incidence of Cervical Ribs After Ovarian Hyperstimulation in Mice. *Animal Biology*, vol 56, No. 1, pp. 63-68 (2006). See Appendix D for full text.

prevent opponents from explaining in the state Voters' Guide that the measure involved human embryo cloning, requiring thousands of women's eggs.[14]

Although efforts to keep this information out of the Voters' Guide failed, the heavily funded campaign nevertheless successfully undermined broader public dialogue on this issue. It did so by incorrectly characterizing all opposition to the measure as motivated primarily by concern with the moral status of the embryo. To the very limited extent that the term "cloning" entered the discussion, it was invariably inaccurately termed "therapeutic cloning," in spite of the fact that no therapies have yet been associated with SCNT. It was not until the election was over that the press began to raise many of the ethical problems implicit in the initiative.

A series of recent legal developments have fueled scientists' reluctance to confront ethical difficulties with SCNT. In 1980, the U.S. Supreme Court, in *Chakrabarty v. Diamond,* affirmed a right to patent genetically engineered life forms.[15] In the same year, Congress passed the Bayh-Dole Act, which allowed universities and their researchers to patent even those research products funded by the federal government.[16] As a result, the field of embryonic stem cell research has become the focus of a virtual biotech gold rush, inevitably creating gross conflicts of interest.

These conflicts of interest have been built into the structure of the newly established California Institute of Regenerative Medicine (CIRM). For example, at least half of its inaccurately named governing board (Independent Citizen's Oversight Committee [ICOC]) represent institutions likely to conduct stem cell research. In addition, at least seven of the 29 ICOC members have significant business relationships, including substantial equity investments and board memberships, with companies involved in stem cell research.[17]

California's Stem Cell Initiative campaign illustrates how the need to secure massive amounts of funding has led advocates to obscure major scientific and technical obstacles to the research. These include difficulties in restricting the potential of embryonic stem cells to desired differentiated types, as well as their tendency to form tumors in adult hosts.[18]

Disclosures to women who are being asked to take significant risks to their health and fertility by making altruistic donations of eggs should not be limited to acknowledging potential negative consequences to the donor's health. They should also reveal the researchers' intent to develop patents using these donated eggs and the potential of these patents to harm the public health and to impede other research. These problems with patenting have been described in detail by Andrews.[19]

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[14] Memorandum of Points and Authorities in Support of Petition for Writ of Mandate and Alternative Writ of Mandate/Order to Show Cause. (7-28-04, Case No. 04C501015) Paul Berg, Robert Klein, and Larry Goldstein, Petitioners vs. Kevin Shelly, Secretary of State of California, Respondent, Geoff Brandt, State Printer; Bill Lockyer. Attorney General of California ; Tom McClintock; H. Rex Green; John M. W. Moorlach; Judy Norsigian; Francine Coeytaux; Tina Stevens; Does I through X, inclusive, Real Parties In Interest. See also Declaration of Dr. Stuart A. Newman, PhD. In Opposition to Petition for Writ of Mandate and alternative Writ of Mandate/Order to Show Cause.

[15] 447 U.S. 303(1980).

[16] For the Bayh-Dole legislation see, Government Patent Policy Act of 1980, Pub. L. No. 96-517, 94 Stat. 3019.

[17] Reynolds and Darnovsky, Reynolds, J. and M. Darnovsky, et al. *The California Stem Cell Program at One Year: A Progress Report.* Center For Genetics and Society. January 2006, p 26. http://www.genetics-and-society.org

[18] Newman, S. A. (2003). Averting the Clone Age: Prospects and Perils of Human Developmental Gene Manipulation. *J. Cont. Health Law and Policy* 19, 431-463.

[19] See Appendix E. Andrews, L.B. "Genes and Patent Policy: Rethinking Intellectual Property Rights." Nature Reviews/Genetics, Vol. 3, October 2002.

Until financial conflicts of interest are brought under control we can expect the pursuit of profit to trump humanitarian concerns in determining the directions science takes. We also can expect continuing challenges to established ethical norms. The conflicts of interest and pressures that existed for Dr. Hwang and his colleagues, two of whom were American, are not unique to Korea. They operate very strongly within the borders of the United States as well.

Some liberal and progressive supporters of stem cell research who are concerned with preventing these abuses have argued that what is needed is "public sector bodies with the power to establish and enforce comprehensive regulations that apply to both publicly and privately funded research."[20] They call for prohibitions on payments to egg providers except for out-of-pocket expenses to prevent the emergence of a market in eggs, a requirement that egg extraction be carried out by those not involved in stem cell research, and follow-up medical care to treat adverse reactions that women who provide eggs suffer.

However, due to rampant conflicts of interest among those involved in the field, I have serious doubts that any regulatory structure could avoid implicitly condoning SCNT, and therefore it would be ineffective in protecting women's health. Proposed regulations are particularly silent on the long-term threats to the health of egg providers, for which researchers must be held responsible.

As a society we are at a turning point in our relationship to science. We are being asked to make women the servants of biotechnology, rather than insisting on a biotechnology that promotes the well-being of all people. For these reasons, until we understand more fully its human costs, I strongly urge your support for a moratorium on SCNT.

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[20] Reynolds, J. and M. Darnovsky, et al. The California Stem Cell Program at One Year: A Progress Report. Center For Genetics and Society. January 2006, p 17. www.genetics-and-society.org

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Evolutionary conserved structures as indicators of medical risks: increased incidence of cervical ribs after ovarian hyperstimulation in mice

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Abstract—The presence of a rib on the seventh cervical vertebra (a cervical rib) represents one of the most common intraspecific variations of the number of cervical vertebrae in mammals. Cervical ribs are highly associated with stillbirths, congenital abnormalities and embryonal tumours. These associations indicate strong stabilising selection against such a change to the highly conserved number of cervical vertebrae in humans. We propose, therefore, that the presence of variation for this highly conserved trait can be used as an indicator of medical risks. We have tested for prolonged effects of controlled ovarian hyperstimulation treatments (OHS) in mice by analysing the frequency of cervical ribs in the offspring of females that had received OHS treatment. We found that OHS treatment in mice had several significant effects on the offspring after adjusting for multiple pregnancy: these included an increase in cervical rib incidence, gestational period and nest size, and a decrease in birth weight and ossification, indicating growth retardation.

The high incidence of cervical ribs in the OHS group compared to the control group (39.5% vs. 4.7%) indicates that the OHS treatment affects embryogenesis during a period that is highly sensitive to disturbance, the early organogenesis stage (phylotypic stage). This implies that in mice OHS treatment of the mother has a prolonged effect and continues during early pregnancy.

Keywords: cervical ribs; evolutionary conservation; homeotic transformation, IVF; organogenesis; ovarian hyperstimulation; Barker hypothesis.

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INTRODUCTION

The number of cervical vertebrae is remarkably constant in mammalian species and is nearly always seven. Nonetheless, variations frequently occur within species and there is, therefore, extremely low interspecific variation, as well as high intraspecific variation (Galis, 1999). We have earlier hypothesised that conservation of the number of cervical vertebrae is due to strong selection against changes of this number due to association with negative pleiotropic effects (Galis, 1999; Galis and Metz, 2003). The presence of cervical ribs (a transformation of the seventh cervical vertebra into a thoracic one, hence a decrease in the number of cervical vertebrae) is one of the most common anomalies in human stillbirths and occurs in up to 50% of stillborn foetuses (Noback and Robertson, 1951; Meyer, 1978; Galis et al., subm.). This implies strong selection against variation in the number of cervical vertebrae. In addition, cervical ribs in humans are associated with an increased incidence of abnormalities and cancer (Gladstone and Wakeley, 1931-1932; Narod et al., 1997; Schumacher et al., 1992; Galis and Metz, 2003). In mice, cervical ribs can be induced at embryonic days 7-8 (Abdulrazzaq et al., 1997), at the beginning of the sensitive early organogenesis stage (Galis and Metz, 2001). Cervical ribs, therefore, appear to be a good indicator of disturbances of early organogenesis that presumably lead to medical risks.

Controlled ovarian hyperstimulation (OHS) in humans is frequently used in ovarian stimulation and ovulation induction to enhance the chance of becoming spontaneously pregnant, but also as part of assisted reproductive technologies. Assisted reproductive technologies are frequently associated with an increased frequency of spontaneous abortions, congenital anomalies, low birth weight, preterm birth and perinatal mortality, albeit with a low prevalence (Helmerhorst et al., 2004; Jackson et al., 2004; Bonduelle et al., 2005; Hansen et al., 2005). Similar abnormalities have been found for OHS treatment alone (Olivennes et al., 1993; Brinton et al., 2004). A low birth weight, often reflecting a disturbance early in life, is associated with cardiovascular diseases later in life (Holt, 2002; Phillips, 2002), an association first hypothesised by Barker (Barker, 1992). In addition, early embryogenesis is, in general, the most sensitive period for disturbances (Galis and Metz, 2001). Ovarian hyperstimulation and other assisted reproductive techniques, therefore, may disturb early embryogenesis, including the very sensitive phase of early organogenesis. To investigate possible effects of OHS treatments on early embryogenesis, the frequency of cervical ribs in the offspring of female mice with and without OHS treatment was measured, and used as an indication of disturbance of early embryogenesis.

MATERIALS AND METHODS

Virgin adult female CD1 mice (8-10 weeks, Charles River, Germany) were randomly assigned to the different experimental groups and mated with randomly assigned CD1 males. Each male mated only once. Females were used irrespective of

the day of the cycle and 142 were intraperitoneally injected with Metrodin (purified urinary hFSH; 5 units in 0.1 ml saline; Serono, Coinsins, Switzerland) at 12:00 and 48 h later with Pregnyl (urinary hCG; 5 units in 0.1 ml saline; Organon, Oss, The Netherlands). Control females (n = 115) received saline injections. Females were examined every morning for vaginal plugs indicating fertilisation (day of detection was considered as embryonic day (E.D. 0)). After birth the mother and newborn mice were weighed. For the control group 115 females were exposed to males, and for the OHS group 142, resulting in 38 (33.04%) and 53 (37.32%) conceptions, respectively. For the experiments, nests of five females were used for each group. Directly after birth, newborn mice were euthanised (peritoneal Nembutal injection), fixed in 4% formaldehyde and stained in a 0.2% silver nitrate solution for 2 weeks. X-ray photographs were taken (15 A, 20 kV, 20 s) and analysed for the number of cervical and thoracic vertebrae. X-ray photographs with insufficient staining were excluded from analysis. All animal experiments were in accordance with governmental guidelines for care and use of laboratory animals and approved by the Animal Care Committee of the University of Leiden.

RESULTS

The OHS group had a more than eight-fold increased incidence of cervical ribs compared to the control group (39.5% of OHS-treated mice showed cervical ribs vs. 4.7% in the control group, $\chi^2 = 19.14$, df = 2, $P < 0.01$, table 1). Part of the increased incidence of cervical ribs was due to the larger litter size in the OHS group, as there was a significant positive correlation between the incidence of cervical vertebrae and the weighted average of litter size between nests from the OHS group ($R^2 = 0.12$, df = 1, $F = 48.52$, $P < 0.01$). The OHS treatment was responsible for at least part of the increased incidence of cervical ribs, because there was also a significant increase in the smaller nests of the OHS group (within the size range of the control group) compared to those of the control group (Log Linear Model, $G^2 = 9.32$, df = 1, $P < 0.01$, litters <20 individuals).

The duration of pregnancy was longer (10.32%) in the OHS group than in the control group (ANOVA, df = 1, $F = 177.99$, $P < 0.001$, table 1) but, despite the longer pregnancy length, there were no significant differences in weight of the offspring (Pearson = 0.032, $P > 0.05$) and growth was thus slower in the treatment groups. Females from the OHS group had a significantly, although only moderately, larger average litter size (32.46%) compared with the control group (control litter size = 15.25, OHS litter size = 20.20, ANOVA, df = 1, $F = 22.88$, $P < 0.01$). In the OHS group the average weight of an individual at birth was negatively correlated with the litter size, but not in the control group (OHS group: $R^2 = 0.74$, df = 1, $F = 134.28$, $P < 0.01$, control group: $R^2 = 0.024$, df = 1, $F = 1.45$, $P > 0.1$). The absence of a litter size effect in the control group may have been due to the smaller size of the nests, i.e., there may be a threshold before litter size negatively affects weight.

Table 1.
Effects of OHS treatment on mice.

	OHS (N)	Control (N)	df	*F*	*P*
Incidence of cervical ribs in the total number of offspring per group (OHS and Control)	39.53% (n = 62)	4.65% (n = 61)	2	$\chi^2 = 19.14$	<0.01
Average duration of pregnancy, days (mean value ± standard error, SE)	20.96 ± 1.46 (n = 5)	19.0 ± 0 (n = 5)	1	177.99	<0.001
Average litter size (mean value ± SE)	20.20 ± 7.10 (n = 5)	15.25 ± 3.23 (n = 5)	1	22.88	<0.01
Average weight of siblings, grams (mean value ± SE)	1.39 ± 0.31 (n = 111)	1.43 ± 0.15 (n = 79)	1	6.97	<0.01
Average weight of mothers, grams (mean value ± SE)	38.78 ± 0.18 (n = 6)	35.57 ± 0.43 (n = 5)			
% new-born mice not analysed (rejection X-ray photographs, delayed ossification)	44.14% (n = 111)	22.78% (n = 79)	2	$\chi^2 = 21.77$	<0.01

The OHS treatment had an effect on individual weight. When comparing the weighted average individual nestling weight, corrected for the influence of litter number on litter weight, the weight at birth of individuals was significantly lower (2.80%) in the OHS group than in the controls (General Linear Model, df = 1, $F = 117.098$, $P < 0.01$).

Significantly more individuals from the OHS group could not be analysed compared to the control group (93.42%) due to insufficient staining of the X-ray photographs, indicating a delay in ossification at birth in the OHS treatment group (44.1%, $N = 111$ vs. 22.8 %, $N = 79$, $\chi^2 = 21.77$, df = 2, $P < 0.01$, table 1). The delay in ossification appears to be due to a direct effect of the treatment itself, because in the OHS group there was no significant difference in rejection rate of photographs between larger litters (larger than the average litter size for the control group, >15) and smaller ones (ANOVA, df = 1, $F = 2.96$, $P > 0.05$). Furthermore, in the smaller litters of the OHS group the rejection rate was also higher than in the control group (49.1% vs. 22.8%, respectively). However, this difference was not significant, presumably due to the low number of small litters in the OHS group (ANOVA, df = 1, $F = 3.26$, $P > 0.1$).

DISCUSSION

OHS treatment with urinary gonadotrophins in mice resulted in a significant increase in the frequency of cervical ribs in the offspring. In addition, we observed a prolonged gestational period, an increased litter size and a low birth weight, in agreement with earlier results on the effect of OHS treatment in mice (Ertzeid and

Storeng, 2001; Van der Auwera and D'Hooghe, 2001; Sibug et al., 2002, 2004). The prolonged gestational period and low birth weight in the treatment group indicate growth retardation. Ossification was also delayed by the OHS treatment, as apparent from the diminished response to silver nitrate.

In mice, cervical ribs are induced at E.D. 7 and 8, during the early organogenesis stage (Abdulrazzaq et al., 1997). The high frequency of cervical ribs, therefore, indicates that the OHS treatment affects early embryogenesis, a period that is highly sensitive to teratogenesis (Galis and Metz, 2001). This implies that, at least in our experiments with mice, the OHS treatment of the mother has a prolonged effect and continues during the early vulnerable stages of pregnancy. Although the response of mice to the OHS treatment may be different from those of humans undergoing OHS treatment, it is possible that similar processes take place in humans. The high incidence of cervical ribs in our experiments and the many associations of cervical ribs with serious abnormalities in humans suggest that these data may have implications for the use of OHS treatments in humans.

We propose that more general variations of highly conserved traits such as the number of cervical vertebrae and the number of digits (see Galis et al., 2002) may be useful as indicators of medical risks.

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To whom it may concern:

I am a former Chief Medical Officer of the Food and Drug Administration (FDA), as well as physician, Board Certified Pathologist, past researcher in genetics and developmental biology, author of *FDA Inside and Out*, and President of Medical Device Assistance, Inc., a regulatory and clinical consulting firm. I personally have been involved in drug, biotechnology and device human clinical trials and am familiar with United States requirements for ethical biomedical conduct. I write this memo for scientists, physicians, legislators, press, and public health advocates who have an interest in SCNT research. I strongly urge that sound ethical and medical practices are adopted regarding the manner in which eggs will be extracted from healthy women donors. Important facts for you to consider:

1. Although it is common practice in IVF facilities to extract eggs as part of infertility treatment, many of the drugs used during these procedures have not been adequately studied for long term safety, nor do some of these drugs have FDA approval for these specific indications. This is not widely understood and has led to significant misunderstanding about the risks involved for women who donate eggs, whether for reproductive purposes or for SCNT research.

Pharmaceutical firms have not been required by either the government or physicians to collect safety data for IVF drugs regarding risk of cancer or other serious health conditions despite the drugs having been available in the United States for several decades. Lack of FDA approval and/or review of these drugs as part of egg extraction procedures should be a major concern of anyone considering SCNT research.

2. The long term health risks for a woman receiving IVF drugs for egg retrieval are unknown.

A woman undergoing IVF stimulation today to conceive a child has accepted that there are "unknown" long term health risks to her body from the stimulation drugs but accepts the risks in terms of a potential benefit to conceive a child. The risk versus benefit calculation for a healthy woman providing her eggs for stem cell research is not the same.

The FDA has approved some of the stimulation drugs specifically for IVF stimulation. IVF stimulation approval was based on bioavailability studies in small numbers of healthy female volunteers, and studies of single cycle exposure in small populations of infertile women. There was no requirement for long-term follow up.

Regarding potential acute short-term risks which have been seen in stimulation trials submitted to FDA, severe Ovarian Hyper-Stimulation Syndrome (OHSS) occurs rarely - in about 3-8% of patients. This condition that results from over-stimulation of the ovary can progress rapidly to a serious life-threatening condition days after completion of egg collection. Based on symptoms, it is classified as mild (7%) or moderate to severe (1%). OHSS has been associated with death and has been reported in women with polycystic ovaries, in younger women, and in women with high estrogen hormone levels and after a woman receives either GnRH agonist or hCG. OHSS carries an increased risk of clotting disorders, kidney damage, and ovarian twisting. Ovarian stimulation in general has been associated with serious life threatening pulmonary conditions in FDA trials including thromboembolic events, pulmonary embolism, pulmonary infarction, cerebral vascular accident (stroke) and arterial occlusion with loss of a limb and death.

Risks of the egg retrieval procedure, although rare, include death, respiratory or cardiac arrest, brain damage, paraplegia, paralysis, loss of function of a limb or organ, hemorrhage, allergic reaction, and infection Bleeding or other injuries which occur during retrieval may require an invasive surgical procedure to correct and could affect future fertility.

Regarding the unknown long term risks, studies to date have not ruled out a possible link between stimulation drugs and an increased risk of ovarian cancer. All stimulation drugs are Pregnancy X - which means they are contraindicated for use in women that are pregnant due to a lack of information regarding the safety of these drugs during pregnancy.

As a scientist, physician, former FDA official, and clinical trial consultant, I understand why some have expressed enthusiasm for SCNT. However, as a physician, I cannot condone SCNT at the expense of a woman's health without giving her an opportunity for adequate informed consent and establishing a mechanism to ensure her safety. Women, scientists, policy makers, physicians, and funding organizations should require that pharmaceutical firms first disclose the actual FDA approved indications for drugs as well as all available safety data before multiple egg extraction from healthy female donors is pursued. All drug data should be reviewed by a neutral, knowledgeable, and independent oversight body whose sole purpose is to protect the safety and rights of healthy women wishing to participate in egg donation. Once such basic drug safety data have been gathered and reviewed, and a regulatory framework and monitoring system are in place, the risks and benefits of SCNT for healthy women can be better assessed.

In the meantime, extraction at the time of an ovariectomy or a tubal ligation offers a far safer and more ethical approach to begin collecting eggs for SCNT research. Even single egg extraction with natural cycling (no hormonal manipulations of the ovary) would be safer than conventional egg extraction procedures.

Additionally and importantly, any woman willing to provide eggs for research should have her own physician - someone not involved in any way with the research or the research institution and whose only job is to look out for the well-being of the woman.

Finally, there needs to be a mechanism in place for long-term follow-up regarding the health of women egg donors. This follow-up must be mandatory, and also under the aegis of the independent monitoring body. Such follow-up of the health of IVF donors has NOT yet been conducted by pharmaceutical firms or IVF physicians despite the long availability of these drugs and technology in the United States.

In conclusion, there is an unfortunate and false assumption of the public, legislators, press and physicians that all current IVF stimulation drugs have been scientifically recognized as "safe" by the FDA and suitable for use in healthy women for multiple egg extraction. That simply and sadly is not correct.

From a purely practical perspective, those promoting SCNT research may be unknowingly tackling a far more costly and serious health burden by allowing the expanded use of current IVF stimulation drugs for SCNT. It is wiser to first require pharmaceutical firms supplying the IVF drugs to provide adequate long term safety data.
It is in the best interests of everyone - including patients, researchers and potential egg donors - for all women contemplating donating their eggs to be treated according to the highest ethical and medical standards, and for their rights and safety to be protected.

Thank you,

Suzanne Parisian, MD

OPINION

Genes and patent policy: rethinking intellectual property rights

Lori B. Andrews

Concerns about human gene patents go beyond moral disquiet about creating a commodity from a part of the human body and also beyond legal questions about whether genes are unpatentable products of nature. New concerns are being raised about harm to public health and to research. In response to these concerns, various policy options, such as litigation, legislation, patent pools and compulsory licensing, are being explored to ensure that gene patents do not impede the practice of medicine and scientific progress.

Although gene patents have been granted worldwide for several years, the wisdom of this action is now being questioned. Lawsuits, proposed legislation, international protests and even patent-office proposals have recently been initiated to eliminate, undermine or otherwise challenge the scope of patents on human genes. The challenges come from various interested parties — people from whom patented genes have been isolated, researchers who wish to undertake genetic epidemiological studies or to develop gene therapies, clinicians and health-care providers who cannot afford expensive licensing fees for genetic tests and policy-makers who want to ensure that the patent system actually meets its goal by encouraging invention. Evidence is mounting that gene patents are inhibiting important biomedical research, interfering with patient care and provoking criticisms from international trading partners.

So far, the US Patent and Trademark Office (USPTO) and the European Patent Office (EPO) have treated isolated and purified nucleotide sequences as if they were the same as man-made chemicals[1] (BOX 1). Although many believe that human genes should not be viewed with such a cavalier attitude[2,3], recent challenges to gene patents have moved beyond the initial moral concerns about making a commodity out of a part of ourselves. Now, the concerns are being expressed in terms of harm to public health and research. These concerns have generated debate and the exploration of policy options to ensure that gene patents do not impede the practice of medicine and the progress of science.

In my view, the decision to allow patents on human genes was inappropriate, both legally and as a matter of sound policy. The useful properties of a gene's sequence (such as its ability to encode a particular protein or its ability to bind to a complementary strand of DNA for diagnostic purposes) are not ones that scientists have invented, but instead, are natural, inherent properties of the genes themselves. Moreover, in my opinion, gene patents do not meet the criteria of non-obviousness, because, through *in silico* analysis, the function of human genes can now be predicted on the basis of their homology to other genes. In addition, as a matter of policy, human nucleotide sequences should not be patentable, even if their function is known, because such scientific information should be available to all.

The foundation of patent law

Industrialized nations worldwide share a belief in the importance of a strong patent system. Such a system was put in place in the United States two centuries ago in the US Constitution to create incentives for technological innovation. Article I of the US Constitution gives Congress the power "to promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries". Because the constitutional provision is vague, the US Congress determines the types of incentive that are necessary to encourage invention and ensure that the public receives a sufficient benefit from the temporary monopoly granted to the inventor.

Under US federal patent law, an inventor has the right to exclude others from making, using or selling his or her invention for 20 years from the date of the application. For a gene to be patented, the patent applicant must show that his or her invention is useful, non-obvious and novel. The usefulness of the inventions must be specific, substantive and "credible". The patent application must also be adequately "enabling". That is, it must describe the invention fully, in a way that would allow another person who is skilled in that field to reproduce the invention. This requirement is particularly important because one of the purposes of patent law is to ensure that the public gets information in exchange for the monopoly granted to the patent holder. When a patent is granted, the information in it becomes public. Other inventors can then use that information to further their own research. Other inventors, however, cannot make or use the patented invention itself without the permission of the patent holder. In the United States — unlike in Europe — the inventor has no duty to actually "work" (use or develop) the invention.

The US patent laws are designed to ensure that the public benefits from a new invention in exchange for the monopoly. The laws do

Box 1 | **The legal basis for gene patents**

Although products of nature are not patentable, various courts have upheld patents on isolated and purified natural substances. The 1912 case of Parke-Davis versus H. K. Mulford[38] upheld a patent on adrenaline, a natural hormone that was found in animal glands. The patent applicant identified, isolated and purified the active ingredient — adrenaline. This created a product that did not exist in nature in that precise form and that could be used for medical treatment.

The US patent office holds that a human gene as it occurs in nature cannot be patented. However, if a DNA sequence is purified and isolated in the form of a cDNA or is part of a recombinant molecule or vector, then this 'invention' is patentable under the precedent of the adrenaline case[1].

not allow patents on products of nature because the public would not be gaining anything new. Also, patents are not allowed on scientific formulas. As the US Supreme Court has pointed out, "The laws of nature, physical phenomena, and abstract ideas have been held not patentable. Thus, a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E = mc^2$; nor could Newton have patented the law of gravity. Such discoveries are 'manifestations of ... nature, free to all men and reserved exclusively to none' "[4].

Genes straddle the boundary between patentable and unpatentable substances. As Rebecca Eisenberg, Professor of Law at the University of Michigan, USA, notes, "DNA sequences are not simply molecules, they are also information. Patent claims to information — even useful information — represent a fundamental departure from the traditional patent bargain" [5]. That bargain originally allowed a patent on an invention in exchange for the disclosure of useful information in the application to spur on other inventors.

Effects on diagnosis and treatment

Gene patents have attracted capital investment to the biotechnology industry. That makes business sense, but not, in my view, policy sense. The very exclusivity of a patent — the monopoly power of its holder — has created problems in medical and scientific fields. For 20 years from the date that a gene patent was filed, gene-patent holders can control any use of 'their' gene; they can prevent a doctor from testing a patient's blood for a specific genetic mutation and can stop anyone from doing research to improve a genetic test or to develop a gene therapy based on that gene.

For example, Athena Neurosciences, Inc., which holds the patent on a gene that is associated with Alzheimer disease — the apolipoprotein E (*APOE*) gene (US Patent No. 5,508,167) — will not allow any laboratory except its own to screen for mutations in that gene[6]. Doctors and laboratories across the country face a lawsuit if they try to determine whether one of their patients carries this genetic predisposition to Alzheimer disease, even though testing can easily be done by anyone who knows the sequence of the gene, without using any product or device made by the patent holder.

In 2001, the US company Myriad Genetics was granted a European patent related to the *BRCA1* breast-cancer-associated gene. The patent (EP699754) covers all methods for diagnosing breast cancer by comparing a patient's *BRCA1* gene with the *BRCA1* gene sequence that Myriad describes in its patent[7]. Myriad is now asserting that no French doctor or scientist should be allowed to test for *BRCA1* gene mutations; instead, the company requires that all samples be sent to Myriad's laboratory[8]. However, French physicians are concerned that such a mandate compromises patient care. They allege that Myriad's test only assesses 10–20% of potential *BRCA1* mutations[9]. Indeed, a French physician has recently identified a mutation in an American family that the Myriad test had missed[9]. Moreover, geneticists in France can offer genetic tests for breast cancer for less than the US $2,680 fee per test that is charged by Myriad. It is both the breadth of Myriad's *BRCA1* patent and the company's refusal to grant licenses for *BRCA1*-mutation detection that has led to concerted and international opposition.

Exclusivity in diagnosis can also impede research. Various mutations in the same gene can cause a particular disease. But companies that do not let anyone else screen a gene sequence that they have patented for other mutations lessen the chance of other disease-associated mutations being found, as often occurs when many laboratories screen the same gene. In countries where the *APOE* gene that is associated with Alzheimer disease and the *HFE* gene that is associated with haemochromatosis have not been patented, researchers have found previously unknown mutations[10,11], which can be used to diagnose people who would not otherwise be diagnosed.

Companies now also sequence and patent the genes of disease-causing bacteria and viruses. This gives them the power to prevent others from introducing inexpensive public health genetic testing for a common infectious disease, for example, or from undertaking genetic research on the disease. The possibility of patenting human genes and the genomes of disease-causing bacteria and viruses has led Tufts University policy professor Sheldon Krimsky to comment that "the intense privatization of biomedical knowledge that has evolved since the 1980s threatens the entire edifice of public health medicine"[12].

Gene patents also hamper pharmacogenomic research. Many drugs work on only a percentage of patients who use them. Genetic testing can help to distinguish those patients for whom a drug will work from those for whom it will not. But such tests will also reduce the market for certain drugs. For example, a pharmaceutical company, GlaxoSmithKline, Plc, has filed for a patent on a genetic test to determine the effectiveness of one of its drugs, but will not develop the test, or let anyone else develop it, possibly because such a test would cause the company to lose customers[13].

Research to find additional genes that are responsible for diseases is also impeded by gene patents. In one reported example, the search for a gene that is related to autism was impeded because researchers from several prominent American universities would not share DNA samples from affected children and their families; each university wanted to capitalize on being the one to discover and patent the gene that is associated with the disease[14]. In response, families of patients with autism founded Cure Autism Now (CAN), which, through its fundraising efforts, has raised US $5 million to create a DNA bank, called the Autism Genetic Resource Exchange, that is available to all scientists who are willing to work on finding the gene or a cure for autism.

Gene patents also undermine the scientific method. Researchers who discover and patent genes have financial incentives to promote the use of those genes for diagnostics as rapidly as possible, sometimes before sufficient data are available to assess how well a test predicts future disease. The patent examiner has to take what the applicant says as correct, and there is no Food and Drug Administration review in the United States when a company offers a genetic test as a service. If a patent holder states that one in three people in the population have the gene

mutation that is covered by its patent, the patent holder can actually prevent others from duplicating the patent holder's research and evaluating it. In one survey, 14 out of 27 gene-patent holders said that they would require a license for researchers to study the prevalence of mutations in the patented gene in the population[15]. Even if the patent holder allows research by other scientists, the licensing costs might prevent other researchers from doing the necessary epidemiological studies to determine, for example, the proportion of people in the general population who carry a gene mutation and who will actually develop the disease. Some entities that offer patented genetic tests have already apparently exaggerated the prevalence of certain diseases, possibly to scare people into being tested[16].

Economic effects on research

Patenting genes can impede invention and health care in other ways too. Gene patent holders have prevented some researchers from searching for cures for genetic diseases. A researcher who wants to find a cure for breast cancer would have to negotiate with not only the patent holder for the full wild-type *BRCA1* and *BRCA2* genes, but with all of the other patent holders who have discovered and patented any of the hundreds of other mutations in these genes.

The granting of patents on parts of genes or different alleles creates a tangle of rights that can impede innovation. It is the policy of the USPTO that the discoverer of a gene should not be able to undertake mutation testing or the development of a product that is based on that gene without the permission of the holders of any patents on expressed sequence tags (ESTs) created from that gene[1]. The EST patent holder could withhold consent entirely or charge a fee. According to John Doll, Director of Biotechnology Examination at the USPTO, "The USPTO views this situation as analogous to having a patent on a picture tube. The picture-tube patent does not preclude someone else from obtaining a patent on a television set. However, the holder of the picture tube patent could sue the television set makers for patent infringement if they use the patented picture tube without obtaining a license"[1]. But I find this analogy troubling. Other inventors can create alternatives to the picture tube, and a consumer can do without a television. There are no alternatives to the patented human genes in genetic diagnosis and gene therapy — and these inventions might mean the difference between life and death to the consumer.

> "'Patent claims to information — even useful information — represent a fundamental departure from the traditional patent bargain' ... [that] allowed a patent on an invention in exchange for the disclosure of useful information in the application to spur on other inventors."

Michigan law professors Michael Heller and Rebecca Eisenberg have discussed how patents can deter innovation in biomedical research by stifling research innovations early on in the product development process[17]. Economist Carl Shapiro elaborates on the problems created by a 'patent thicket'. Using traditional economic analysis, he has shown how, when several monopolists exist that each control a different raw material needed for development of a product, the price of the resulting product is higher than if a single firm controlled trade in all of the raw materials or made the product itself[18]. However, the combined profits of the producers are lower in the presence of complementary monopolies. So, if there are several patent holders whose permission is needed to create a gene therapy (and any one of them could block the production of the gene therapy), inefficiencies in the market are created, potentially harming both the patent holder and the patent users.

Gene patents do not seem to be necessary to encourage technology transfer in the move from gene discovery to the availability of a genetic diagnostic test. As soon as information about the discovery of the haemochromatosis gene was published, laboratories began testing for mutations in the gene. After a patent on the gene was granted 17 months later, 30% of the 119 US laboratories that were surveyed reported discontinuing or not developing a genetic test for the disease[19]. The patent holder was asking for an up-front fee of US $25,000 from academic laboratories and as much as US $250,000 from commercial laboratories, plus a fee of US $20 per test[19]. The patent interfered with clinical use of the test and potentially compromised the quality of testing by limiting the development of higher quality or lower cost testing methods[19].

Professional organizations, such as the American College of Medical Genetics[20] and the College of American Pathologists, oppose gene patents as threatening medical advancement and patient care[21]. The World Medical Association considers human genes to be part of "mankind's common heritage" and urges medical organizations around the world to lobby against gene patenting[22]. This mounting concern about gene patents has lead to policy initiatives through litigation, legislation and administrative action.

Litigation

In the United States, the patent system is a three-way relationship among the USPTO, the courts and the Congress. All three have roles to ensure that the goals of the patent system are met and that the monopoly granted is not too broad. Most often, this means that the courts and the Congress reduce the breadth and scope of patents granted by the USPTO. For example, when Samuel Morse convinced the USPTO to grant him a patent on all uses of electromagnetic waves, the Supreme Court ruled that he could not patent every conceivable use of electromagnetic waves[23]. He could only patent his invention — the telegraph.

In addition, the Director of the USPTO has the authority to order patents to be re-examined. In the 1970s, the USPTO denied patents on software. When, in 1981, the US Supreme Court ruled that software was patentable subject matter[24], the USPTO lacked examiners with expertise in this area to evaluate these types of patent and, as a result, issued many patents that were criticized as being over-broad[25]. In response, the USPTO undertook more than 40 re-examinations of software patent claims that it had issued. These re-examinations resulted in the rescission of existing claims and the establishment of rules to narrow markedly the scope and breadth of these types of patent claim in the future.

There has yet to be a definitive legal case to address directly whether human genes are an appropriate subject matter for a patent in the first place. Rather than challenging the patenting of genes *per se*, the court cases on gene patents are generally battles between two entities (such as a university and a biotech company) about who has rights to a particular patent. There is no incentive for either side to challenge whether a gene patent is an inappropriate patent on a product of nature because each side wants to reap the financial rewards of a gene patent. The member of the public who could end up paying a high fee to learn genetic information about himself or herself — or be denied

that information altogether — rarely has legal standing in the United States to bring a lawsuit to challenge the patentability of human genes. Although a physician, researcher or laboratory could challenge the patentability of human genes, various financial and institutional constraints have generally acted against this. Legal challenges against patents are financially expensive. A physician challenging a patent can expect to pay upwards of US $500,000 in attorneys' fees alone[26]. For a laboratory, it might be cheaper to pay for a license to use a gene — and pass that cost on to the patients who are tested — than to initiate a legal challenge.

Consequently, it is quite remarkable that any court challenges to gene patents are taking place. However, recently, legal assaults on gene patents were launched on two fronts. The first type of case was brought by patients against researchers and their institutions in cases in which the defendants did not specifically disclose their intentions to patent a gene that they isolated from their patients. The patients rely on precedents that require physicians/researchers to disclose potential financial conflicts of interest to the patient/research subjects in advance of undertaking the research[27]. One such suit, concerning the aspartoacylase gene, which is mutated in Canavan disease — a rare, genetic, neurodegenerative disorder that occurs most frequently in Ashkenazi Jewish families — is now pending in the federal court in Chicago. (I am a public interest (pro bono) attorney for the plaintiffs in this case.)

The second type of legal challenge, typified by that mounted by the French, contests aspects of the patentability of genes and raises policy concerns about the effects of gene patents. In October 2001, the Institut Curie in France challenged Myriad Genetics' European patent (EP 699754) on the *BRCA1* gene on the grounds of alleged lack of novelty (because predisposition tests for breast cancer on the basis of indirect methods were available before the Myriad patent); lack of inventiveness (as the gene sequence that was patented by Myriad was based, in part, on information from public genome databases); and inadequate description (because there were errors in the original sequence published by Myriad)[9] (see online link to the Institut Curie). On 22 February 2002, the Institut Curie initiated a challenge to another Myriad patent, EP 705903, on *BRCA2*. The governments of Belgium and the Netherlands intend to challenge that same patent as well (see online link to the Institut Curie). Geneticists in those countries issued a joint statement that, if gene patents were not narrowed or eliminated, "the monopolies on genes and genetic testing will wreck the reimbursement system and negatively influence health care."

Other challenges to gene patents might also try to narrow the claims that are made in patent applications. In some cases, the patent applicant has been granted rights not only to the mutations in a gene that he/she discovered, but also to any other mutations discovered later by other researchers. In other instances, the patent gives the applicant rights to all possible functions of the encoded proteins. In still other cases, patents have been granted on all methods of comparing the sequence of a high-risk individual with a known normal sequence, even though the patent has only described one method. The breadth of such patents could be challenged on the grounds that the patent has not sufficiently described all of the mutations, functions or methods that the patent holder has claimed rights to.

Legislation

Because the US Constitutional provision encouraging inventors is quite general, the actual provisions of patent law are enacted by Congress and can be modified by that body. It is not uncommon for the US Congress to limit patent rights in the public interest[28]. For example, a statute gives the federal government 'march-in' rights[29]. When a federally funded patentee has not made the invention available to the public within a reasonable time or when "action is necessary to alleviate the health or safety needs which are not reasonably satisfied" by the patentee, the government can license the patent to third parties. In addition, under the Clean Air Act, courts can, when necessary, order compulsory licensing of patents on equipment or technology used in air pollution control on reasonable terms to ensure competition[30].

The US Congress is considering a proposed law (BOX 2), introduced by Members of Congress Lynn Rivers and Dave Weldon (a physician), which would amend the federal patent statute to exempt health-care providers that are involved in genetic testing from patent infringement liability, so that their ability to diagnose patients is not compromised by gene patents. Also, because there is no statutory research exemption to patent infringement in the United States (and because rare exemptions that have been recognized by the courts have been extremely narrow), the bill, if passed, would allow non-commercial researchers to be exempt from liability for the use of patented genes. It is quite common internationally to have exceptions to patent laws. For example, the European Patent Convention Article 53(a) prohibits patents for "inventions the exploitation of which would be contrary to 'ordre public' or morality." Other inventions that the European Union's Biotechnology Directive consider to be unpatentable include processes for cloning human beings; processes for modifying the germ line of human beings; and uses of human embryos for industrial or commercial purposes[31].

Box 2 | **US legislative initiatives to reform patents on genes**

On 14 March 2002, members of the US Congress Lynn Rivers and David Weldon proposed a new law that would exempt health-care providers who carry out genetic testing from being sued by holders of patents on genes. This proposed bill, the Genome Research and Diagnostic Accessibility Act of 2002 (REF. 39), aims to exempt two groups from patent infringement: first, medical practitioners and related health-care entities that provide genetic diagnostic, prognostic or predictive tests; and second, scientists that undertake non-commercial genetic research. The bill also requires that patent applications involving a genetic sequence discovered with federal funds are made public within 30 days of a patent application being filed[39].

Rivers and Weldon also introduced a companion bill — the Genomic Science and Technology Innovation Act of 2002. This proposed bill directs the Office of Science and Technology Policy (OSTP) to initiate a study of the effect of federal policies on the discovery and development of genomic technologies. This proposed bill is based on the presumption that federal intellectual-property laws and technology-transfer laws can stimulate the development of innovative genetic technologies by attracting commercial investment, but might also inhibit basic research and information sharing, thereby slowing innovation. Rivers' primary concern in drafting this bill was to assess whether gene patents are granted without an adequate understanding of their impact on innovation. The aims of this study are: to assess the impact of federal policies, including intellectual-property policies, on the innovation process for genomic technologies; to identify and quantify the actual and expected effects of patenting policy on genomic science and technology innovation; and to consider various alternatives for protecting intellectual property rights over genomic materials and their likely impact on genomic innovation.

Exceptions in patent law to protect patients' access to health care and to protect doctors' liability have a historical basis in the United States. Originally, US patent law forbade patents on health-care inventions. Throughout the first 150 years of US history, the USPTO did not issue patents for methods used to diagnose and treat patients[26]. Such methods were not considered to be patentable subject matter by the medical profession, by the courts or by the USPTO because patents were granted for tangible inventions. Medical or surgical methods were not considered to fall in the scope of the statutory requirements until 1954, when the Board of Patent Appeals opened the door to patents on medical methods[32]. In the 1990s, such patents began to interfere with patient care. In 1996, the US Congress created an exception in the patent law so that health-care providers are not subject to patent infringement suits when they use a patented medical or surgical technique[33]. Eighty other countries already had such an exemption[34]. Until recently, many other countries did not even provide intellectual property protection to medicines and other pharmaceutical products[35]. Some developing countries had short periods of protection for such products (such as three years of patent protection in Thailand) to allow health needs to be met by the rapid introduction of generic drugs[35].

The Trade-Related Intellectual Property Rights (TRIPS) agreement of the World Trade Organization, promulgated in 1995, requires all of its international signatories to agree to provide a 20-year intellectual property protection for inventions (including those that are related to health care). But even TRIPS highlights how public health should be given greater weight than the commercial concerns of patentees. Article 27 of TRIPS specifically allows governments to exclude diagnostic, therapeutic or surgical methods from patentability. It also allows them to deny patentability of a particular invention to protect human life or health. Article 8 of TRIPS allows governments to take public health concerns into consideration in their national intellectual property laws, and Article 31 allows governments to ignore health-care patents in certain situations and to grant compulsory licenses (see next section) to third parties to produce a generic version of a health-care product. Under TRIPS, patents can be ignored in a public health emergency.

Patent pools and compulsory licensing

Policy options based on traditional patent law are also being explored, such as creating a patent pool — an agreement between two or more patent owners to license one or more of their patents to one another or to third parties. Patent pools are voluntary agreements among patent holders in which they gather all the necessary tools to practice a certain technology in one place, rather than obtaining licenses from each patent owner individually. One model to base this on is the pool created by the American Society of Composers, Authors and Publishers (ASCAP), which handles the licensing of music under copyright laws. Instead of having to negotiate with each holder of a copyright for thousands of songs, a radio station or bar can buy a blanket license from ASCAP and play any song from the pool at any time. In a similar way, a gene patent pool could extend non-exclusive licenses to all for set fees.

> "...court cases on gene patents are generally battles between two entities (such as a university and a biotech company) about who has rights... [t]here is no incentive ... to challenge whether a gene patent is an inappropriate patent on a product of nature because each side wants to reap the financial rewards..."

Patent pools are particularly appropriate when patent exclusivity is being used contrary to the public's interest. During the First World War, the Assistant Secretary of the US Navy, Franklin D. Roosevelt, pressured the aircraft industry to form a patent pool to facilitate the production of aeroplanes[18]. Previously, the Wright–Martin Aircraft Company and the Curtiss Airplane and Motor Company were able to block such production owing to their control of key patents.

Compulsory licensing is also being explored as a way to counter some of the problems of gene patents. This system has been advocated by the French Minister of Research, Roger-Gérard Schwartzenberg (see online link to Institut Curie). Compulsory licensing is the granting of a license by a government to use a patent without the patent holder's permission. This approach, which might be necessary if gene patent holders did not voluntarily create patent pools, would require gene patent holders to allow physicians, researchers and others to use the patented gene sequence for a reasonable fee. Laboratories would be able to undertake genetic diagnostic testing using their own, as well as patented, tests, which could lead to the discovery of new mutations. Furthermore, pharmaceutical companies would not be able to prevent pharmacogenomic testing related to their products. Also, researchers could not be prevented by gene patent holders from undertaking research on gene therapies (or discouraged from undertaking such research through high licensing fees).

Compulsory licensing is clearly permissible under TRIPS, and the mere threat of it sometimes serves to drive down the costs of pharmaceuticals. When the South African government passed the Medicines and Related Substances Control Act in December 1997 to authorize the compulsory licensing of drugs, 40 drug companies initiated a lawsuit to overturn the act[36]. Subsequently, the companies agreed that the law could be enforced, dropped the legal challenge and negotiated to sell their products at a lower cost[37].

Conclusion

Whatever policies society develops for gene patents, policymakers will be influenced by the fact that the 'bio' in biotechnology — the genes in the gene patents — comes from people. Researchers need the trust of those whom they study to get access to their tissue for research into diagnostics and cures. Using the biological resources of the public (and a substantial amount of public funding), genes have been discovered and patented. Now, policy makers are being asked to ensure that the public receives the benefits.

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Online links

DATABASES
LocusLink: http://www.ncbi.nlm.nih.gov/LocusLink
APOE | aspartoacylase | *BRCA1* | *BRCA2* | *HFE*
OMIM: http://www.ncbi.nlm.nih.gov/Omim
Alzheimer disease | Canavan disease | haemochromatosis

FURTHER INFORMATION
American College of Medical Genetics: http://www.acmg.net
College of American Pathologists: http://www.cap.org
Cure Autism Now: http://www.canfoundation.org
European Patent Office: http://www.european-patent-office.org
Food and Drug Administration: http://www.fda.gov
Institut Curie: http://www.curie.fr
Trade-Related Intellectual Property Rights: http://www.wto.org/english/tratop_e/trips_e/trips_e.htm
US Patent and Trademark Office: http://www.uspto.gov
World Medical Association: http://www.wma.net
World Trade Organization: http://www.wto.org
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SCIENCE AND SOCIETY

Human genetic technologies, European governance and the politics of bioethics

Brian Salter and Mavis Jones

With human genetic technologies now an important area of European research and development, bioethics is becoming increasingly important in its regulation and future. As regulatory decisions are also statements about who should get what, bioethics cannot avoid political controversy. Can bioethics sustain its claimed role as authoritative adviser to decision makers, or will its attempts to reach a consensus on human genetic technologies be perceived as the actions of an ambitious interest group? What, in short, is its political future in Europe and elsewhere?

In a 2002 report that outlines a strategy for the life sciences and biotechnology in Europe, the European Commission recognizes a fundamental tension at the heart of its policy. On the one hand, Europe has the scientific and industrial potential to be a global leader in new biotechnologies, including human genetic technologies. On the other hand, it acknowledges that "public support is essential, and ethical and societal implications and concerns must be addressed" if Europe is to benefit from these technologies[1]. Given the European public's reaction to genetically modified food and crops, there is no guarantee that the problems that beset one area of biotechnology will not affect another. When it comes to human genetic technologies, such as pharmacogenetics, gene therapy, predictive diagnostics and therapeutic cloning, will the necessary public support be there? It remains to be seen whether the health applications of genetic knowledge will be perceived by the public as being an issue that is distinct from GM food and crops[2].

Traditionally, public support for new technologies has been assured through governmental regulatory arrangements that have relied heavily on scientific advice about the risks that are associated with a particular technology. However, the public response to the bovine spongiform encephalopathy (BSE) crisis in the United Kingdom (when conflicting scientific advice was withheld from the public until it was too late to quell the epidemic, resulting in a subsequent wide-scale inquiry) and to GM crops in Europe and Asia (where public protests about GM foods, including the occasional destruction of seeds and crops, have achieved results such as mandatory product labelling) is testament to the general decline in the public's trust in scientific authority[3–6]. Ethical and cultural concerns have been thrown to the fore and new forms of public opposition[7–9] have emerged to challenge the efficacy of what is sometimes called "the technocratic approach" to regulation. Given the uncertainties that therefore beset this science-based approach, 'red' biotechnology, as the health genetic technologies are sometimes known, could prove to be as contentious as the 'green' biotechnologies of food and crops.

With the European Union's plan to expand its investment in genomics and

Ladies and Gentlemen

I am the mother of Jacqueline Rushton who died as a direct result of in vitro fertilisation treatment in the Rotunda Hospital, Dublin,Ireland, on the 14th January 2003. I have never spoken in public before and hope you will appreciate how this is a very daunting task for me. I feel I owe this to my beloved daughter Jacqui whose only wish was to have a baby.

She put herself into the hands of experts and she lost her own life in her attempt to give life. These words were spoken at her funeral by the priest. At that time we knew something had gone terribly wrong, but had not got the knowledge we now have. She wanted her story told.

Jacqueline was a beautiful girl in every way. She was a healthy fit thirty-two year old who was longing for a baby. Her dream was to have a big family and stay at home at home and look after them.

In 2002 she went to her local G.P. to discuss fertility problems. It was discovered that Jacqui was not ovulating properly, that was her problem. She was referred to the Fertility Unit at the Rotunda Hospital in Dublin.

She and her husband paid 3,000 euro to the clinic and in November 2002 Jacqui commenced I.V.F. treatment. This meant inhaling a drug to put her into a false menopause. She forgot to take it one day while out shopping with her sister and laughingly said as she inhaled at the bus stop, 'Oh! I hope people won't think I'm a drug addict '.

She was excited about the prospect that she might find out that she was pregnant on Christmas Day, God love her!

She had to inject herself daily with Puregon, the ovarian stimulating drug. On day eight, 3rd Dec, her levels of estradial were three times higher than the highest level in the range.

There were two possible treatment options available:

To cancel or to cut down the drug and coast.

At no time were they told to cancel. Only coasting was advised which they did. By cutting down the estradial it was hoped to bring down the levels to a safe one for the administration of HcG, the drug which releases the egg, and which is the point of no return. They were never shown any figures of safe levels of Estradial or safe numbers of eggs.

I went to hospital with Jacqui on the 3rd Dec. The drug was cut to 100 units puregon. She was feeling very bloated and could hardly walk.

She spent her time in bed the week of the treatment and I brought all her meals up to her. She felt so sore and swollen. Jacqui was saying 'I never thought it would so hard to have a baby.'

On Day ten, but she received no injection, she was so overstimulated. When she went for her scan it showed multiple follicles and the promise of a large amount of eggs. Jacqui thought this was good news, as I did, demonstrating how little we knew about safety levels. I got talking to another girl while waiting. She was also in great distress,but not as bad as Jacqui.

She could not believe how awful a procedure it was turning out to be.

When the nurse came out with Jacqui she said laughingly, 'Oh! Here are the overstimulated ones'. They both had difficulty walking . Poor Jacqui! She was always so good humoured and tried to smile through all her pain.

That evening she even made us bring down the Christmas Tree from the attic. This was always her job and she didn't trust anyone else to get it just right. She had great taste and was very artistic. She sat on the couch and gave all her instructions but eventually she struggled even to kneel down. Her tummy was so tight and it hurt so much.

Jacqui and her husband went to the clinic on day eleven. At 10 o'clock that night Jacqui received the HcG Injection. Only a nurse was present. Her Estradial level was 22,500 pmols, more than twice the safety level. The Authorisation Form was signed by Professor Robert Harrison.

According to the Royal College Guidelines, Jacqui by then had an 80% chance of developing severe ovarian hyperstimulation syndrome, which is life threatening.

On Sunday 8th Dec Jacqui went in for the egg retrieval procedure. 33 eggs were retrieved. When she was brought from the theatre, the other girl who was waiting to go in next told me Jacqui was screaming in pain. It is heartbreaking to hear about your child's suffering.

Most patients go home after egg retrieval and fertilised eggs are implanted two days later in the womb. This couldn't happen for Jacqui. Hers had to be frozen, she was so hyperstimulated.

Everyday till Wednesday we just heard 'Jacqui is not coming home, she has mild hyperstimulation'. One of my daughters phoned me on the Wednesday and said 'Mam, there is something really wrong with Jacqui, she can hardly talk'. I panicked after that phone call and rang the sister in charge and finally got permission to see my daughter.

When I saw Jacqui propped up in the bed, she looked so frail, sick and terrified. She had an oxygen mask clamped to her face. She had a catheter, elastic stockings, a monitor and a drip. I got such a shock I ran over to her and put my arms around her as best I could and said Oh! Jacqui I love you so much. What has happened ? She tried to laugh at me, she hated to worry us. I went home that night and cried and cried. The family wouldn't believe she was that bad. I knew Jacqui was very seriously ill. I felt this awful feeling in my heart she was going to die.

We were being constantly told by Doctors and Nurses, 'She'll be alright. She will pass all this fluid out through her kidneys and she'll be grand. We can only monitor and support the symptoms.'

She just got worse every day. I went in on the Thursday. The other girl had also been admitted by ambulance to the hospital. She too was very ill and breathless but she recovered, thank God.

There have, by the way, been 97 cases of OHSS in the Rotunda between 1999 and 2003.

Jacqui was so ill. No one seemed to care, there was no sense of urgency, and nothing was done. She was filling up with fluid from her ovaries. Her lungs were inundated and her breathing was becoming nearly impossible. She was on a huge amount of oxygen. She couldn't eat, drink, sleep, and was constantly nauseous and breathless. Jacqui told me that every breath she took required every ounce of her energy. Her suffering was horrific.

I went in on Friday 13th Dec in the evening . Her husband and I were still the only visitors allowed. I was demented as her swelling was increasing alarmingly. Nurses bleeped doctors but none came. Finally at 11o'clock a drip was put up.

The next day Jacqui told me she was praying to her Guardian Angel when a passing Doctor noted her condition. She was blue from lack of oxygen and he had her admitted to the High Dependency Unit

On Monday I arrived to find Jacqui being prepared to be sent to the Mater General Hospital. I'll never forget that journey; oxygen mask clamped to her little face, terror in her eyes, she was so cold . The nurse and a young doctor tried to reassure me she'd be alright. None of them seemed to realise what severe O.H.S.S. meant.

In the General Hospital no draining of fluid was done initially. Her catheter was found to have been kinked and that seemed to relieve her slightly. She also got a feeding tube. She felt safer there and thought she would get better.

Her sisters and brothers could now visit. Jacqui's deterioration shocked them to the core. Jacqui said between gulps of oxygen, 'Oh Mam I feel awful, it's not getting any better'. Her husband arrived then and we had to go. She looked at me and said 'Mam don't go'. She just looked at us going out the door with her beautiful brown eyes. That was the last time we spoke to Jacqui.

Later that night we got a summons from the hospital. Her husband Danny, her Dad and I rushed in. Only her husband was allowed in. She was being put into a drug induced coma and being placed on a ventilator.

On Christmas Eve we all visited. She looked peaceful and rested on the ventilator. But on the 25th Dec her Dad and I were distraught when we saw her. She looked like a little waxen doll. I cried and said to the doctor and nurse who didn't seem to understand us, 'My daughter is going to die in this hospital'.

We were all sent for at 7o'clock the next morning. They had tried to move her in the bed and the fluid had moved over her heart. She had crashed. They revived her with adrenalin. That day over two litres of fluid were drained from her lungs, 23 days after admission. She had put on over two stone with the fluid.

We spent every minute at her side. Her brother Daniel stayed there nearly constantly praying holding her hand and willing her to live. Jacqui was very religious and had all her little tattered prayer leaflets with her.

But all Jacqui's organs were slowly destroyed. She had five holes in her lungs, five chest drains draining into five horrible buckets around her bed. Her kidneys started to fail, she couldn't take any nutrition, she was on industrial doses of antibiotics. Next we were told her eyes were fixed indicating brain damage They couldn't close her eyes with the swelling from the fluid, so her eyes had to be taped shut. Eventually her strong heart gave out and all the machines were switched off.

She died at 12 o'clock noon a slow agonising death from O,H.S.S. She had 33 eggs recovered, even though the safe level is well under 20. Five embryos survived; five little potential babies. They were baptised and were buried with Jacqui.

This is the nightmare that happened to my daughter who only wanted to have a baby. This is what we had and have to endure for the rest of our lives. Our carefree family life is gone, Jacqui is missing, destroyed by by unsafe I.V.F. treatment.

We as parents didn't know anything about I.V.F. or its dangers and felt it was the couple's own business what they did, and that we couldn't interfere. Our only worry was that they'd be disappointed if it didn't work.

I want to thank my family for all their research and help since Jacqui's death. They didn't want me to do this as it is so hard. My gut feeling was this is what Jacqui would have wanted, she was a fighter like me and I want justice, she deserves it.

After three nerve wracking inquests, we got a verdict of Medical Misadventure. The professional conduct of the consultant, Professor Robert Harrison, is now being investigated by the Fitness to Practice Committee of the Irish Medical Council.

At her enormous funeral some of the nurses attended. One of those wonderful human beings hugged me close and said its going to be very hard. I knew she meant the grief, and the quest for justice in Ireland, where you have to be a multi-millionaire to get it.

A girl who goes for I.V.F. treatment for infertility, is no different in effect from a girl choosing to donate her eggs for altruistic or financial reasons. They both have to go through the same invasive horrific drug-based treatment.

Why is natural fertility treatment not offered to patients? It should be available as a choice. It is much safer with no drugs. This is the truth. There is indeed an alternative to these harmful drugs, and couples could have their longed for babies, without the pain and risks which cost Jacqui her life.